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REVIEW

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Pregnancy related pharmacokinetics and antimicrobial prophylaxis during fetal surgery, cefazolin and clindamycin as examples

Karel Allegaert[1,2,3] | Anouk E. Muller[4,5] | Francesca Russo[1,6] | Sam Schoenmakers[7] | Jan Deprest[1,6,8] | Birgit C.P. Koch[3]

[1]Department of Development and Regeneration, Cluster Woman and Child, KU Leuven, Leuven, Belgium

[2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

[3]Department of Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

[4]Department of Medical Microbiology, Haaglanden MC, The Hague, The Netherlands

[5]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands

[6]Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium

[7]Department of Obstetrics and Gynecology, Erasmus University Medical Center, Rotterdam, The Netherlands

[8]Institute for Woman's Health, University College London, London, UK

Correspondence
Karel Allegaert, Department of Development and Regeneration, Cluster Woman and Child, KU Leuven, Herestraat 49, 3000 Leuven, Belgium.
Email: karel.allegaert@uzleuven.be

Abstract

Antimicrobial prophylaxis during surgery aims to prevent post-operative site infections. For fetal surgery, this includes the fetal and amniotic compartments. Both are deep compartments as drug equilibrium with maternal blood is achieved relatively late. Despite prophylaxis, chorio-amnionitis or endometritis following ex utero intrapartum treatment or fetoscopy occur in 4.13% and 1.45% respectively of the interventions.

This review summarizes the observations on two commonly administered antimicrobials (cefazolin, clindamycin) for surgical prophylaxis during pregnancy, with emphasis on the deep compartments. For both compounds, antimicrobial exposure is on target when we consider the maternal and fetal plasma compartment. In contrast, amniotic fluid concentrations-time profiles display a delayed and much more blunted pattern, behaving as deep compartment. For cefazolin, there are data that document further dilution in the setting of polyhydramnios. Along this deep compartment concept, there is some accumulation during repeated administration, modeled for cefazolin and observed for clindamycin. The relative underexposure to antimicrobials in amniotic fluid may be reflected in the pattern of maternal-fetal complications after fetal surgery, and suggest that antimicrobial prophylaxis practices for fetal surgery should be reconsidered.

Further studies should be designed by a multidisciplinary team (fetal surgeons, clinical pharmacologists and microbiologists) to facilitate efficient evaluation of antimicrobial prophylaxis.

1 | INTRODUCTION

The purpose of antimicrobial prophylaxis during surgery is to minimize colonization of micro-organisms at the surgical site(s) throughout the procedure to minimize or prevent surgical site infections (SSI).[1] The antimicrobial (drug choice, dose selected) administered should hereby ensure adequate serum and tissue (subcutaneous or other relevant compartments) concentrations from incision, throughout, and until shortly after surgery. This means that we should consider the micro-organisms (*Staphylococcus aureus* as reference pathogen, but coagulase-negative staphylococci [CoNS] may also be involved) relevant to the site of surgery and their pharmacodynamic target.[1,2]

These general concepts obviously also apply for surgical interventions during pregnancy, including fetal surgery. However, pregnancy-related changes like the increase in glomerular filtration, cardiac output and total body volume, changes in body composition and protein binding, as well as specific compartments of interest, like the fetal compartment and amniotic cavity should be taken into account as

these changes affect pharmacokinetics.[2-5] These are deep compartments, that is, body compartments where drug equilibrium is achieved relatively late. As the data on time-concentrations profiles are limited, other commonly performed surgical interventions provide at least some information on the pharmacokinetics and target attainment in some of the relevant compartments.

The most commonly performed surgical intervention during pregnancy is a cesarean section. In the Center for Disease Control (CDC) 2017 update on surgical prophylaxis, a clear position on the timing of antimicrobial administration (before incision) was taken.[1] When prophylactic antibiotics (any time) were compared to no prophylaxis during cesarean section, there was a significant reduction in the incidence of wound infection (RR 0.40, 95% CI 0.36-0.46), endometritis (RR 0.38, 95% CI 0.34-0.42) and other serious maternal infectious complications (RR 0.31, 95% CI 0.20-0.49).[6] Administration of antibiotics (eg, cefazolin, clindamycin) before skin incision in women undergoing cesarean section further reduced the risk of endometritis, and also wound infection compared to those who received antibiotics after neonatal cord clamping.[1,7,8]

The antibiotics commonly administered for surgical prophylaxis do cross the placenta to result in fetal co-exposure.[3,4,9] Within the setting of prophylaxis for cesarean delivery, this is unintended but there is evidence that this does not result in short-term adverse health effects for the newborn. In contrast, there is still debate and an active research line on the question if perinatal antimicrobial exposure modulates the long-term risks for allergy-related syndromes, like eczema, asthma or auto-immune diseases, with alterations in the neonatal gut microbiome as claimed mechanism.[9]

However, risk reduction does not imply that infections do not occur. In the most recent Cochrane review on the impact of antimicrobial prophylaxis on post-cesarean infections, the incidence of maternal febrile morbidity, wound infection, endometritis and other serious infectious complications were still 12,3%, 3.4%, 5.7% and 0.5% respectively in the prophylaxis group.[6] In a recent study comparing the rate of SSIs in women undergoing cesarean delivery, cellulitis was more common in women exposed to clindamycin + gentamicin (900 mg + 5 mg/kg) (adjusted odds ratio 1.93, 95% CI 1.03-3.31, 4.7 vs 2.4%) when compared to cefazolin (2-3 g).[10]

Fetal surgery includes procedures on the umbilical cord, the placenta or membranes, and/or the fetus with also relevant differences in duration and extent or invasiveness of surgery. For fetal surgery, commonly used dosing regimens for antimicrobial prophylaxis are cefazolin, 2 g 8qh for 24 hours, or clindamycin, 900 mg 8qh for 24 hours, initiated "shortly" before surgery. Furthermore, some surgeons administer an additional dose (eg, cefazolin [500 mg], 600 mg clindamycin [600 mg], 500 mg nafcillin [500 mg], vancomycin [500 mg], ampicillin [4 g], oxacillin [400 mg]) in the amniotic cavity at the end of more complex and prolonged fetal surgical procedures, like fetal repair of spina bifida or fetal tumor resection.[11,12]

This review aims to summarize the observations on cefazolin and clindamycin pharmacokinetics as most commonly administered antimicrobials for prophylaxis during pregnancy, with specific emphasis on the compartments relevant to fetal surgery (fetus and amniotic cavity) to illustrate the fragmented and limited information. We briefly introduce these compound specific findings by describing the impact of pregnancy on the pharmacokinetics of antimicrobials. Following the discussion of these compound specific findings (cefazolin, clindamycin), we suggest a research approach and the available tools to make progress in the field of antimicrobial prophylaxis for fetal surgery.

What's already known about this topic?

- Various practices of antimicrobial prophylaxis during fetal surgery have been reported.
- However, chorio-amnionitis or endometritis following ex utero intrapartum treatment or fetoscopy occur in 4.13% and 1.45% respectively of the interventions, without available data on the most effective strategies for antimicrobial prophylaxis.

What does this study add?

- Based on limited data during fetal surgery, concentrations-time profiles for cefazolin and clindamycin in the maternal and fetal compartments are on target, while these profiles in the amniotic fluid compartment display a delayed and more blunted pattern, resulting in suboptimal amniotic exposure.
- This suggests that we should study these practices to reconsider dosing regimens to potentially improve outcomes. Such studies should be designed by a multidisciplinary team (fetal surgeons, clinical pharmacologists and microbiologists) to facilitate efficient evaluation of antimicrobial prophylaxis.

1.1 | Pharmacokinetics of antimicrobials during pregnancy

It is reasonable to assume similar antimicrobial pharmacodynamics during pregnancy when compared to the non-pregnant setting.[13] Related to these pharmacodynamics, three patterns for targeted and effective pharmacotherapy have been defined, depending on the antimicrobial mechanisms to attain maximal bacterial killing. These patterns are either (i) the fraction of time (duration) that an antimicrobial remains above a target minimal inhibitory concentration (MIC) threshold (beta-lactams, including cefazolin), (ii) the peak antimicrobial concentration above a given concentration or (iii) a mix of both, with the area under the concentration-time curve divided by a target (as for vancomycin or clindamycin).[13]

Consequently, similar exposure of antibiotics should be aimed for, integrating the pregnancy related aspects of pharmacokinetics in dosing regimens. Many of the anatomic and physiologic changes observed during pregnancy will result in marked changes in *a*bsorption, *d*istribution, *m*etabolism and *e*limination (ADME), collectively referred to as pharmacokinetics. It is hereby important to stress that pregnancy is not a dichotomous factor, and that changes are not uniform, but evolve over the consecutive trimesters of pregnancy. Some of these changes in maternal physiology of relevance to PK of antimicrobials for the consecutive trimesters of pregnancy are further illustrated in Figure 1.

As these antimicrobials are administered by the intravenous route, absorption is only a marginal issue, although fetal absorption from the amniotic cavity may also occur. Distribution during pregnancy can be influenced by changes in body weight, regional blood flows, tissue composition (like body water, body fat), plasma composition and volume and alterations in the unbound fraction of a given antimicrobial. Clearance is driven by metabolism and elimination, with renal elimination (glomerular filtration, renal tubular transport) as the main route of elimination for most antibiotics.[4,5] The glomerular filtration rate increases significantly during pregnancy, predominantly as a consequence of the increased renal blood flow and ultimately also due to single nephron glomerular hyperfiltration (Figure 1).[14] Finally, the antimicrobials commonly used for prophylaxis do cross the placenta, resulting in fetal co-exposure, with a given exposure over time. This includes an equilibration half-life (describing the time lag) between the maternal plasma and the fetal plasma and—when applicable—amniotic cavity. The subsequent impact of these ADME aspects for "model" compounds (cefazolin, clindamycin) will be discussed separately.

1.2 | Cefazolin

Compound and target: Cefazolin is a first generation cephalosporin for intravenous or intramuscular administration. It is the most commonly used prophylactic antimicrobial agent for surgery. For fetal surgery, a commonly used dosing regimen is 2 g.q8h for 24 hours. The European Committee on Antimicrobial Susceptibility testing (EUCAST) mentions a MIC distribution of 0.125-2 mg/L and an epidemiological cutoff (ECOFF) of 2 mg/L for *S aureus*.[15] Consequently, the current minimal targeted cefazolin MIC to treat or prevent *S aureus* infections is 2 mg/L. Obviously, this ECOFF may change over time in the event of emerging resistance.

Pharmacokinetics: Both non-compartmental and compartmental pharmacokinetic (PK) analyses have been performed to describe cefazolin PK in pregnant women, with a wide variety of tissues (eg, blood, adipose tissue or both), drug concentrations (total, unbound or both) and clinical characteristics (obese, non-obese, different gestational ages).[16-18] For this compound, the two main pregnancy related changes are the differences in glomerular filtration rate and in protein binding (Figure 1).[19]

Cefazolin clearance of the *maternal blood compartment* during pregnancy is twice that of healthy young adults, while the equilibration half-life between the plasma and amniotic fluid compartment is 4.4 hours.[20] Maternal administration of 2 g of cefazolin results in therapeutic concentrations in *umbilical cord blood* at delivery (free cefazolin concentration > 8 mg/L) in the newborn for at least 5 hours after delivery, with an equilibration half-life between mother and fetus of about 2 hours.[17] A similar pattern on maternal-fetal exposure with fetal levels in the therapeutic range has been described in case of maternal obesity.[21]

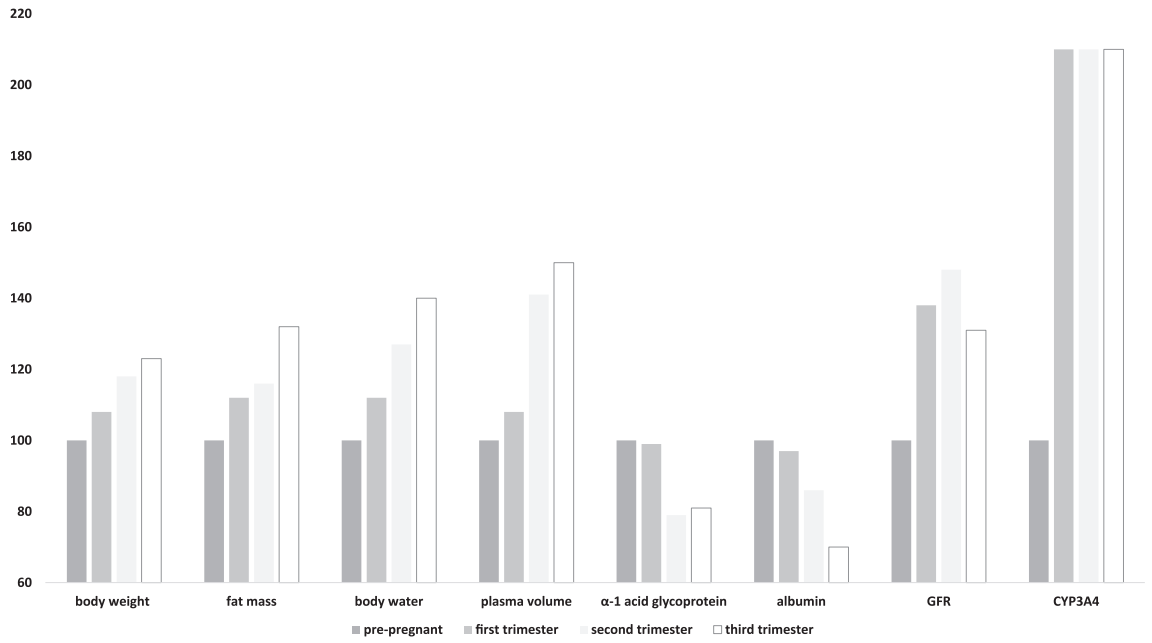

FIGURE 1 Percentage changes in physiologic parameters across the consecutive trimesters of pregnancy compared to the pre-pregnancy setting (100%). Percent changes have been calculated at 12, 24 and 36 weeks based on the individual trend lines as described by Abduljalil et al to reflect the first, second and third trimester. GFR, glomerular filtration rate[5]

In contrast and following the first 2 g dose of cefazolin at the time of fetal surgery (2 g.q8h, 24-48 hours) the median cefazolin concentration in the *amniotic fluid* was 0.62 (*n* = 96 observations, range 0.06-3.73) mg/L. This dataset covers the full gestational age range of relevance to fetal surgery from 17 weeks until term gestational age. Within this age range, cefazolin clearance was not affected by gestational age. However, and of relevance to fetal surgery, in the presence of polyhydramnios (caused by the fetal condition under study in that case), these concentrations were even lower [(0.4 (range 0.12-0.6) vs 1.3 (0.06-3.9) mg/L in the absence of polyhydramnios)].[20] In two of these in utero interventions, fetal urine was simultaneously collected as bladder puncture was part of the scheduled fetal intervention.[20] In both events, fetal urine cefazolin concentrations were significantly higher compared to paired amniotic fluid observations: 1.94 and 5.5, compared to 0.83 and 1.25 mg/L respectively illustrating the contribution of fetal renal clearance to the amniotic cavity cefazolin concentrations. In another cohort of pregnant women at term (elective cesarean, *n* = 18), the mean cefazolin concentration was 1.54 (SD 2.1) mg/L.[22]

Merging the available evidence, the amniotic cavity as deep compartment does not attain the target levels, while the fetal and maternal blood compartments are above the minimal target. Pending on the type of surgery, the antibiotic concentrations reached in the amniotic fluid compartment are of particular interest for fetal surgeons as this is the site where fetal surgery is performed, and inoculation of bacteria may occur. This might be compensated by the practice to inject an antibiotic in the amniotic cavity at the end of more complex and prolonged fetal surgical procedures, like fetal repair of spina bifida or fetal tumors.[11,12]

Clinical practice and efficacy: Clinical practice guidelines based on a review of the earlier mentioned PK evidence in maternal plasma and subcutaneous tissue, and expert opinion recommend to increase the single preoperative prophylactic dose (from 2 to 3 g) before cesarean intervention in obese and morbidly obese patients, but this has not been proven to be of additional benefit in different studies.[1] In the most recent study, La Rosa et al reported on a retrospective analysis and observed an overall low (5%) incidence of SSI, without differences for the higher dose (2 g when body mass index (BMI) <30, 3 g if BMI≥30) vs the regular dose (1 and 2 g respectively) cohort.[23] However, for non-elective (during labor or after membrane rupture) cesarean delivery, extended-spectrum prophylaxis with adjuvant azithromycin (500 mg, intravenous) in addition to "standard" cefazolin dosing resulted in a significant reduction (12%-6.1%) of the composite outcome (endometritis, wound infection or any other infection).[24] There are no data specific on the association of cefazolin exposure and maternal-fetal outcome after fetal surgery.

1.3 | Clindamycin

Compound and target: Clindamycin is a lincosamide antibiotic approved for use in adults and children requiring treatment for staphylococcal, streptococcal or anaerobic infections. Clindamycin binds to the 50S bacterial ribosome subunit to inhibit protein synthesis. Consequently, clindamycin has a bacteriostatic action. The EUCAST ECOFF for *S aureus* is 0.25 mg/L, and for *Streptococci* spp. (including group B Streptococcus) 0.25 or 0.5 mg/L. For gram-positive anaerobes or gram-negative anaerobes, a target value of 4 mg/L is used.[15] Clindamycin efficacy hereby correlates to the area under the concentration curve (AUC) for the free drug concentration divided by the current MIC [$fAUC_{0\text{-}24h}$/MIC].[3,25]

Clindamycin is used to treat infections during pregnancy and its systemic use was classified as Pregnancy category B drug in the former FDA classification (B = no risk in animal reproductive studies,

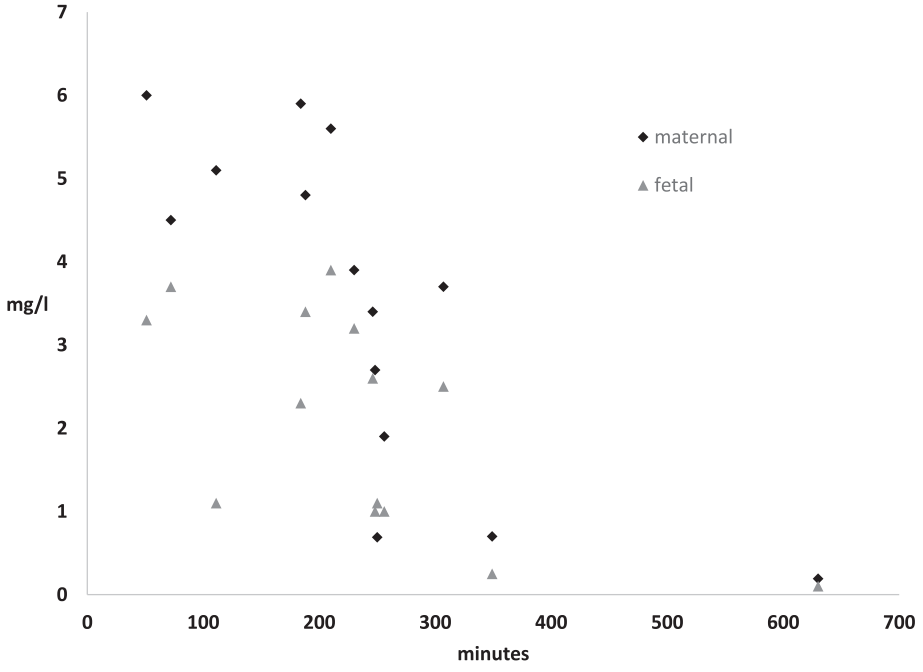

FIGURE 2 Pooled observations of individual paired clindamycin concentrations in maternal plasma (black square) and umbilical cord blood (gray triangle) after first intravenous administration of 900 mg clindamycin to the mother before delivery.[25,31] *X*-axis = time (minutes); *Y*-axis = clindamycin concentration (mg/L)

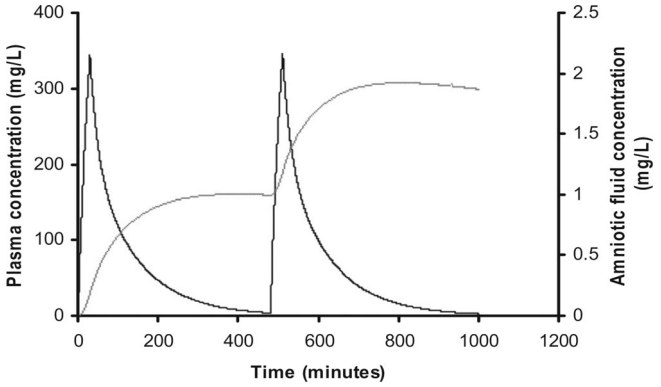

FIGURE 3 Simulation for the maternal plasma and the amniotic fluid compartment in a pregnant patient with polyhydramnios, when 4 g cefazolin were administered with a second dose (4 g) 8 hours after the first dose.[20] *X*-axis = time (minutes); *Y*-axis = clindamycin concentration (mg/L)

because studies in humans cannot rule out the possibility of harm, clindamycin should only be used during pregnancy if clearly needed).[3] The clinical experience includes studies on the adjunctive use of clindamycin to prevent preterm labor and delivery, especially in women with bacterial vaginosis,[26] as well as an alternative for peripartum group B *Streptococcus* prophylaxis in the presence of maternal allergy to penicillins.[27] A teratological study on lincosamides, including clindamycin, suggested that the risk for major congenital anomalies was not increased.[28] This is in line with another cohort of 647 newborns that were exposed to clindamycin in the first trimester of pregnancy.[3,28]

Pharmacokinetics: For clindamycin, pregnancy related changes in body composition and weight, but also changes in alpha-1 acid glycoprotein concentration and CYP3A4 activity matter (Figure 1). Clindamycin is most often administered by intravenous route, but oral administration is also possible because its absorption is rapid and extensive with an estimated bio-availability of 87%.[29] Clindamycin distributes extensively in body fluids and tissues, including bone and capsular tissue, but not the cerebrospinal fluid.[30] It diffuses across the placenta into the fetal circulation and appears in breast milk (breast milk/maternal plasma ratio 0.08-3.1).[25,30-35] The level of protein binding in non-pregnant humans ranges from 62% to 94% and binding relates to the alpha-1 acid glycoprotein concentration.[25] Clindamycin is metabolized to the active *N*-demethyl (cytochrome p450 (CYP)3A4) and sulphoxide metabolites and also some inactive metabolites. These characteristics change throughout pregnancy. About 10% of the drug is excreted in the urine as active drug or metabolites and about 4% in the feces. The remainder is excreted as inactive metabolites. Its elimination half-life is about 2-3 hours in healthy, non-pregnant adults.[3]

At delivery and based on *maternal plasma* observations collected in seven term pregnancies following iv administration (900 mg), the mean estimated clearance was 10 L/h, the elimination half-life was 2.6 hours.[25] After oral administration of a single dose of clindamycin (450 mg, 2.5-6.5 hours before therapeutic abortion) in seven pregnant women (10-22 weeks of gestational age), the maternal peak concentration and the concentration at intervention were 5.16 (2.9-9) and 1.77 (0.68-4.5) mg/L respectively. After repeated oral administration (450 mg.q8h, 4-20 doses, 4.6 [1.8-9] g, with the last dose 3.3-6.3 hours before therapeutic abortion), these maternal plasma concentrations were 6.3 (4.2-10.4) and 2.84 (1.1-5.8) mg/L, respectively.[32]

Four studies reported on the *maternal-umbilical cord blood concentrations* during either single or repeated clindamycin (450-900 mg) iv administration.[25,31-33] Because of the different doses applied and the absence of clinical data on individual maternal weight, we used paired maternal and cord blood clindamycin levels to calculate the fetal/maternal ratio. Based on 33 paired observations extracted from the individual articles, the mean ratio was 0.72 (SD 0.36). This ratio was higher ($P < .05$) during repeated ($n = 14$, 0.8, SD 0.37) compared to single ($n = 19$, 0.6, SD 0.31) dose administration, likely reflecting the fact that some accumulation occurs as the fetal compartment behaves as a deep compartment. Figure 2 provides an overview of the time-concentrations points collected in maternal and umbilical cord blood after single clindamycin (900 mg) administration in 14 cases as pooled from two different studies.[25,31] The pattern suggests that maternal-fetal transfer is fast, but incomplete.[34]

Finally, we could only retrieve data on *amniotic fluid disposition* in the earlier mentioned oral clindamycin study in women undergoing termination of pregnancy.[32] After oral administration of a single dose of clindamycin (450 mg, 2.5-6.5 hours before the procedure) in seven pregnant women (10-22 weeks of gestational age), the amniotic fluid concentration was 0.02 mg/L at intervention. After repeated oral administration (450 mg.q8h, 4-20 doses, 4.6 [1.8-9] g, last dose 3.3-6.3 hours before therapeutic abortion), the amniotic fluid concentration was 0.82 (0.3-1.9) at intervention ($n = 5$), or 1.07 (0.64-1.6) mg/L at delivery ($n = 4$).[32] Similar to cefazolin, the amniotic cavity seems also to behave as a deep compartment and the threshold concentrations (<0.5-4 mg/L) are not always attained, be it that the target for *S aureus* (<0.25 mg/L) is likely reached.

Clinical practice and efficacy: Clindamycin has been extensively prescribed for several decades to prevent or treat infections during pregnancy and in peripartum.[3] The CDC recommended dosage of 900 mg.q8h iv to result in a rapid and steep decline of vaginal group B Streptococcus colony counts (<5% of the colony counts) within the first 2 hours after administration, similar to the decline after penicillin administration.[27] We could not retrieve data specific to the fetal surgery setting.

2 | DISCUSSION

We provided an overview on observations on cefazolin and clindamycin disposition, with specific emphasis on the deep compartments relevant for antimicrobial prophylaxis during fetal surgery. As both compounds have a relative low molecular weight (454.5 and 424.9 g/mol), with reduced pregnancy-related protein binding (albumin and alpha-1 glycoprotein respectively, Figure 1), passive placental

diffusion occurs and results in relevant fetal exposure in the hours after maternal administration.

In contrast, the amniotic fluid behaves for both drugs as a deep compartment, with concentration-time profiles displaying a delayed and much more blunted pattern compared to the maternal and fetal plasma compartment. These concentrations are further diluted in the presence of polyhydramnios. Along this deep compartment concept, there is some accumulation during repeated administration, modeled for cefazolin[20] and observed for clindamycin.[32]

Although based on a limited number of observations, we hypothesize that it is worth the effort to explore the potential clinical relevance of the relative underexposure to antimicrobials in the amniotic fluid, as this may be reflected in the pattern of maternal-fetal complications after fetal surgery. In a recent systematic review and meta-analysis in this journal and based on 10 596 patients, maternal complications were estimated to occur in 6.2% of fetoscopic and 20.9% of open fetal surgeries (serious in 1.7 and 4.5% respectively), but any linkage with antimicrobial prophylaxis practices was not possible.[36] Chorio-amnionitis or endometritis following an ex utero intrapartum treatment procedure occurred in 4.13%, and in 1.45% undergoing fetoscopic surgery, following PROM in 47.8 and 36.3% of these cases, with two additional case descriptions of severe chorioamnionitis with maternal sepsis (one case following bipolar cord coagulation, one case following fetoscopic laser photocoagulation).[36] As also mentioned by these authors, consistent, structured and prospective reporting on maternal complications using the existing registries is needed to properly quantify maternal risks.[36]

Multidisciplinary reflections on the antimicrobial prophylaxis practices during fetal surgery are valuable as part of this need to quantify maternal risks. This should combine fetal surgery expertise, knowledge on microbiology and pharmacometric skills. Pharmacometric skills cover both population pharmacokinetic and physiology-based modeling as very powerful mathematical tools to generate knowledge.

Population PK models enable the analysis and interpretation of dense, unbalanced or even sparse observations to explore covariates in order to (partly) explain inter-individual variability (including pregnancy), to individualize dosing or explore scenarios.[4] To illustrate its potential relevance, we refer to the earlier reported simulations based on the cefazolin dataset collected in maternal plasma and amniotic fluid during fetal surgery.[20] As illustrated in Figure 3, a second dose of cefazolin (4 g.q8h) will result in attainment of the target MIC concentration (2 mg/L) of cefazolin for *S aureus* in the amniotic cavity, even in the setting of polyhydramnios.[20] Alternatively, intra-amniotic injection can be considered, although there are no data yet on its safety. The practice to inject antibiotics in the amniotic cavity exists at the end of open fetal repair of spina bifida.[11,12]

Physiology-based PK (PB-PK) models are "exposure prediction" models consisting of a multiple of differential equations that deterministically simulate or predict drug movements in the body within a physiologically realistic structure. In this structure, tissues and organs are compartmentalized with knowledge of their size and composition.

The different compartments are interconnected through the blood flow and arranged in a parallel circuit to reflect the circulatory system. PB-PK modeling has moved to the front line as a promising approach to ultimately predict the PK in pregnant women prior to initializing clinical trials. Such PB-PK model of renally cleared antimicrobials (cefazolin, cefuroxime, cefradine) has been described, and contains an amniotic fluid compartment.[5,37] Irrespective of the model method applied, in vivo data are needed to further validate such estimates as an intermediate step to confirm adequate antimicrobial exposure as the final outcome step obviously is the incidence of infectious complications.

In conclusion, but based on limited data on both pharmacokinetics and efficacy and safety in this specific setting, we claim that further studies should be designed by a multidisciplinary team (fetal surgeons, clinical pharmacologists and microbiologists) to facilitate efficient evaluation of antimicrobial prophylaxis in the specific field of fetal surgery.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Karel Allegaert https://orcid.org/0000-0001-9921-5105
Francesca Russo https://orcid.org/0000-0002-5029-7899
Jan Deprest https://orcid.org/0000-0002-4920-945X

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